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Stereoselective Glycosylation of 2-Nitrogalactals Catalyzed by a Bifunctional Organocatalyst

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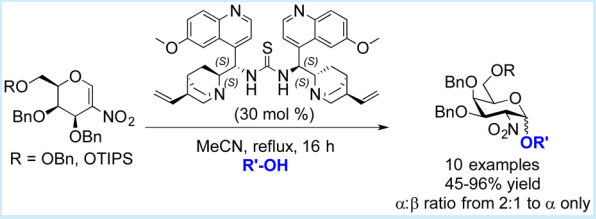
Supporting Information

ABSTRACT: The use of a bifunctional cinchona/thiourea organocatalyst for the direct and α-stereoselective glycosylation of 2-nitrogalactals is demonstrated for the first time. The conditions are mild, practical, and applicable to a wide range of glycoside acceptors with products being isolated in good to excellent yields. The method is exemplified in the synthesis of mucin type Core 6 and 7 glycopeptides.



The stereoselective synthesis of glycosides is still one of the remaining challenges in oligosaccharide synthesis. 2-Amino glycosides, typically present in the *N*-acylated form, are an important class of glycans that are often found as integral components of biologically relevant oligosaccharides and glycoconjugates. In particular, 2-acetamido-2-deoxy-D-*O*-galactopyranosides α-linked to the OH group of serine, threonine, or other glycosides are a common motif in a number of proteins such as mucins, cell membrane glycoproteins, blood group determinants, immunoglobulins, antifreeze glycoproteins, and glycoprotein hormones.[1−4] In addition, 2-amino-2-deoxy-*O*-glycosides are also constituents of several nucleosides and aminoglycoside antibiotics, e.g. streptomycin, kanamycin B, neomycins, paromomycins, kasugamycin, pyranmycins, and lividomycins.[5] Thus, these compounds represent an important synthetic target. However, despite many efforts in the area, the synthesis of 1,2-*cis* aminoglycosides still remains particularly difficult since most common *N*-protecting groups (e.g., amides, carbamates) exhibit 1,2-*trans*-directing behavior during the glycosylation reaction favoring the formation of β-linked products.[6] 2-Nitroglycals have been shown to be useful glycosyl donors for the synthesis of aminoglycosides whereby the nitro group serves as a nonparticipating latent amino functionality.[7−11] Base-catalyzed conjugation of alcohols to 2-nitroglycals has been reported by the Schmidt group for forming α- and β-linked 2-amino-2-deoxy-*O*-glycosides.[12] Moreover, the α/β-selectivity of this concatenation reaction is highly dependent on the nature of the base and nucleophile employed in the reaction.[6,13−16]

Stemming from our interest in the development of novel catalytic systems for the stereoselective synthesis of glycosides,[17−20] we decided to focus our efforts on the organocatalytic preparation of 2-deoxy-2-amino-*O*-galactosides. Herein, we report the development of a mild, efficient, and stereoselective bifunctional organocatalyst for the direct glycosylation of 2-nitrogalactals and its application in the synthesis of mucin type α-*O*-linked 2-acetamido-2-deoxy-glycoconjugates.

Organocatalysis has been successfully applied to the synthesis of oligosaccharides.[15,18−25] Our team reported the use of Schreiner's thiourea to promote the highly α-selective glycosylation of galactals with a number of OH nucleophiles.[20]

In addition, the organocatalytic enantioselective addition of soft carbon nucleophiles and thiols to nitroalkenes has been documented by various research groups.[26−33] A common feature in all the catalytic systems employed in these conjugate addition reactions is the use of bifunctional catalysts that contains both a thiourea and a basic amine group. It is proposed that while the thiourea functionality coordinates to the nitro group, and thus increases the electrophilicity of the nitroalkene, the pendant amine activates and directs the addition of the nucleophile into the prochiral alkene (Figure 1).[26,31,34] We hypothesized that such bifunctional organocatalysts would be ideally suited as mild promoters for the stereoselective glycosylation of 2-nitroglycals.

Our experiments began with a screening of a series of commercial bifunctional cinchona alkaloid/thiourea catalysts for their ability to promote the stereoselective glycosylation of perbenzylated 2-nitrogalactal **1**[12] with glucoside acceptor **2**.[34] As summarized in Table 1, the glycosylation reaction with 10 mol % of urea **3a** or thiourea **3b**[35] in CH_2Cl_2 proceeded with good conversions to product **4**[12] (79−81%) after 48 h, albeit giving an ∼1:1 α:β anomeric mixture (Table 1, entries 1 and 2). Changing the catalyst to the opposite pseudoenantiomer, as in thiourea **3c**,[35] did not cause any significant changes to the yield or stereochemical outcome of the reaction (Table 1, entry 3). It was also observed that the presence of both the (thio)urea and amine functionality were required for activity, as no reaction was

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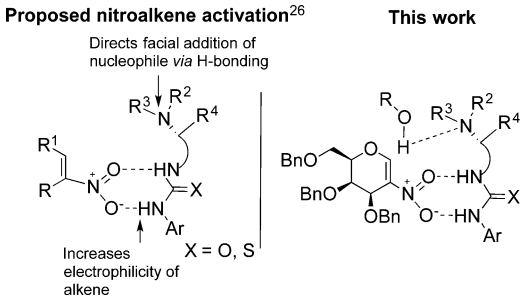
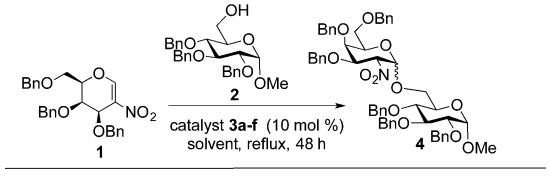
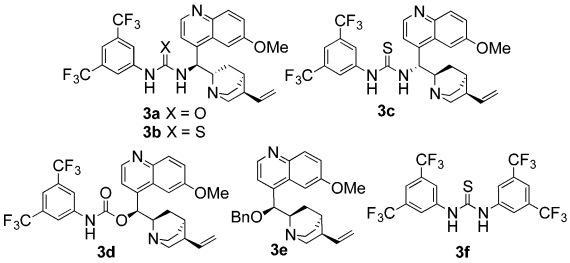


Figure 1. Proposed general activation of nitroalkenes by bifunctional thiourea catalysts.

Table 1. Initial Catalyst and Solvent Screen in the Glycosylation of 2-Nitrogalactal 1





entry	catalyst	solvent	yield (%)[a]	α:β[a]
1	**3a**	CH_2Cl_2	81	0.8:1
2	**3b**	CH_2Cl_2	79	1:0.8
3	**3c**	CH_2Cl_2	80	1:1
4	**3d**	CH_2Cl_2	5	0.9:1
5	**3e**	CH_2Cl_2	16	1:1
6	**3f**	CH_2Cl_2	0	N/A
7	**3b**	THF	66	2.4:1
8	**3b**	$PhCH_3$	78	2.4:1
9	**3b**	$PhCF_3$	85	2.4:1
10	**3b**	1,4-dioxane	75	2.4:1
11	**3b**	MeCN	87	4:1
12	**3b**	DMF[b]	29	1.5:1
13	**3b**	DMSO[c]	0	N/A

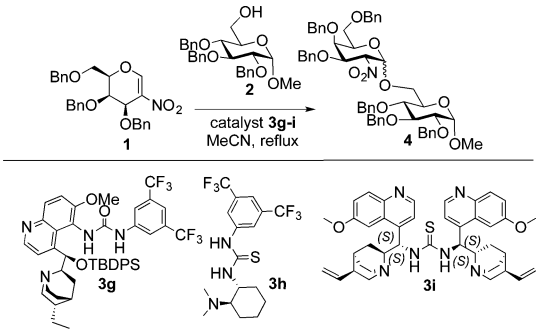
[a]From ^{1}H NMR. N/A = not applicable. [b]Reaction carried out at 82 °C. [c]Reaction carried out at 90 °C. **3a**, **3c**, and **3d** were also screened in MeCN affording 4:1 α:β ratios, while **3e** and **3f** in MeCN yielded little (<15%) or no product, respectively.

observed when using thiourea **3f**[37] and very poor conversions were achieved with carbamate **3d**[38] or cinchona alkaloid **3e**[39] as the sole promoters after 48 h (Table 1, entries 4−6).

Next, we decided to explore solvent effects using **3b** as the model catalyst (see Table 1). Pleasingly, an increase in selectivity toward the desired α-anomer was achieved when using THF, toluene, trifluorotoluene, or 1,4-dioxane as the reaction solvent, with MeCN being the optimum choice affording the product in 87% yield and with an improved 4:1 α:β ratio (Table 1, entry 11). However, reactions carried out in DMF or DMSO were detrimental to the yield and stereocontrol (entries 12 and 13). These results are consistent with MeCN helping to stabilize a transient ion pair intermediate which leads to an enhancement of the stereochemical influence of the catalyst.[40]

To investigate if the spatial presentation of the key functionalities (thio)urea and amine could have an effect on the outcome of the reaction, additional catalysts, C-5′ substituted cinchona alkaloid/urea **3g**,[29] thiourea **3h**,[41] and bis-cinchona alkaloid thiourea **3i**[42] were prepared and subjected to the glycosylation reaction in MeCN at reflux as before. It was found that only thiourea **3i**, (Table 2, entry 3) showed an increase in

Table 2. Catalyst Optimization in the Glycosylation of 2-Nitrogalactal 1



entry	catalyst (mol %)	time (h)	yield (%)[a]	α:β[a]
1	**3g** (10)	48	57	1:0.9
2	**3h** (10)	48	75	3:2
3	**3i** (10)	48	94	4:1
4	**3e** + **3f** (10)	48	50	1:0.8
5	**3i** (10)	24	72	4:1
6	**3i** (20)	24	82	4:1
7	**3i** (30)	24	87	4:1
8	**3i** (30)	16	82	4:1
9	**3i** (50)	24	81	4:1

[a]From ^{1}H NMR.

reactivity (94% conversion after 48 h) and a similar anomeric selectivity toward the α-product as observed with **3b** (Table 1, entry 11). It is important to note that reactions carried out using a 10 mol % 1/1 mixture of **3e** and **3f** in MeCN proceeded in moderate yields of 55% after 48 h and gave an almost equimolar mixture of anomers (entry 4). These results further demonstrate that the 3D architecture of the catalyst is important for both reactivity and stereocontrol.

While it is well-known that cinchona-based thioureas can self-associate at either high catalyst loading or low temperatures and become less active catalysts,[43−46] bis-cinchona alkaloid organocatalysts such as **3i** are designed to prevent any self-association,[42,47,48] which should allow us to increase catalyst loadings in hopes of improving the reaction rate without erosion of diastereoselectivity. Further optimization of the reaction with **3i** (Table 2, entries 5−9) established that a 30 mol % catalyst loading shortened reaction times and glycoside products were obtained in 82−87% yield after 16−24 h (entries 7 and 8), with higher catalyst loadings not offering any further improvements (entry 9).

Having established optimal reaction conditions, our attention was then turned to exploring the scope of the organocatalytic glycosylation using a range of versatile building blocks (Table 3). In general, glycosylations involving glycosyl donors **1** and **5**, which were prepared from commercial D-galactal (see Supporting Information for details), and both reactive and sterically

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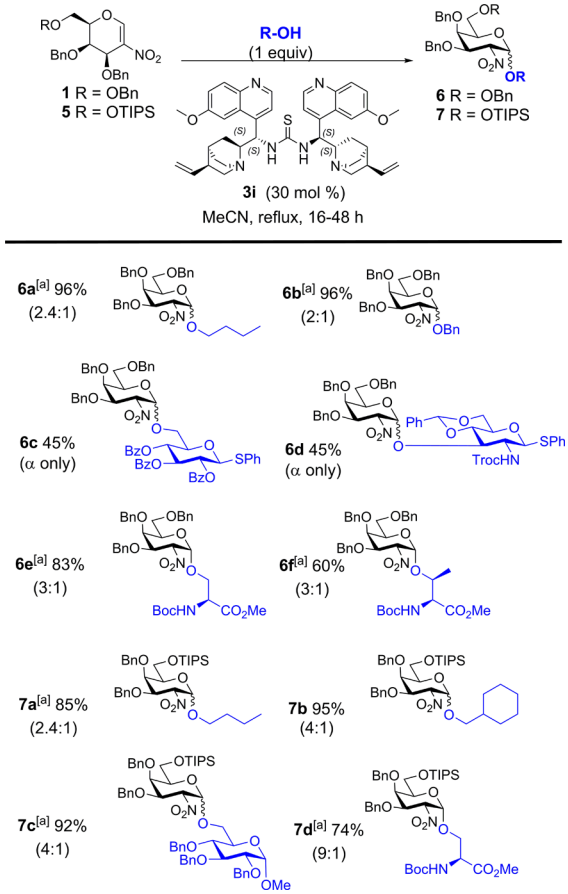
Table 3. Glycosylation of 2-Nitrogalactals 1 and 5 with a Variety of Glycosyl Acceptors

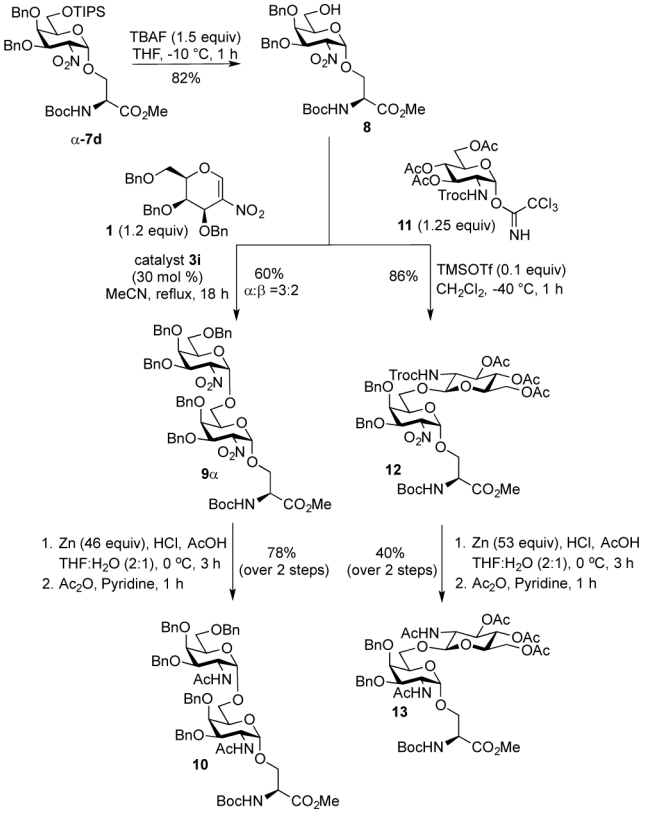


[a]Both anomers were separated by flash column chromatography, see the Supporting Information for details.

hindered acceptors in the presence of **3i** proceeded in moderate to excellent yields within 16−48 h, demonstrating that the catalyst tolerates the presence of acetals, alkenes, ethers, esters, and carbamates. Glycosylations with primary alcohols afforded high yields with a preference for the α-products. Thus, glycosides **6a**, **6b**, **7a**, **7b**, and **7c** were isolated in 96−85% yields and 2:1 to 4:1 α:β ratios. Interestingly, reactions with glycosyl acceptors bearing electron-withdrawing protecting groups afforded disaccharides (**6c** and **6d**) with complete α-stereocontrol, albeit in moderate yields (45%).[49] It is well-established that disarming substituents reduce the electron density of the neighboring hydroxyl group, lowering its nucleophilicity and this has been shown to improve stereoselectivity, as the reaction can be carried out in a more controlled manner.[50] Pleasingly, glycosylations of benzyl-protected **1** with Boc-functionalized serine or threonine proceeded smoothly to give the corresponding glyco-conjugates **6e**[51] and **6f**[14,51] in 83% and 60% yield, respectively, and with a 3:1 α:β anomeric selectivity. It is noteworthy that reaction of C-6 silyl protected galactal **2** and protected serine afforded **7d** with an improved α:β ratio of 9:1 and 74% yield.

To showcase the methodology, the synthesis of mucin-type Core 6 and 7 glycoconjugates[52−54] **10** and **13** was attempted using the developed organocatalytic conditions (Scheme 1). Starting from α-linked 2-nitrogalactoside **7d**, selective silyl ether removal with TBAF afforded monohydroxylated **8** in 82% yield, ready to be glycosylated. Glycosylation of **8** with *O*-benzyl-protected 2-nitrogalactal **1** using 30 mol % of **3i** in MeCN

Scheme 1. Synthesis of Mucin-Type Core 6 and 7 Glycosides 10 and 13



afforded Core 6 disaccharide **9** in 60% yield as a separable 3:2 α:β mixture. The presence of a C-2 nitro group in both the donor and acceptor that can interact with the catalyst may account for the loss of stereoselectivity in this reaction. Reduction of the nitro groups from α-glycoside **9** using Zn/HCl in a mixture of AcOH/THF/H_2O, followed by *N*-acetylation with acetic anhydride in pyridine, furnished target **10** in 78% yield over the two steps. Alternatively, glycosylation of **8** using *N*-Troc-protected glucosamine donor **11** yielded Core 7 disaccharide **12** in 86% yield and with complete β-stereocontrol. Concomitant Zn reduction of the nitro and NHTroc protecting groups in **12** and subsequent *N*-acetylation performed using the same reaction conditions as before afforded **13** in 40% yield over the two steps.

In conclusion, we have described the first application of a bifunctional cinchona/thiourea organocatalyst for the direct and stereoselective glycosylation of 2-nitrogalactals to afford α-*O*-linked-2-amino-2-deoxygalactosides in moderate to excellent yields. The method is mild, practical, and widely applicable to a range of nucleophile acceptors. Furthermore, we have demonstrated the applicability of the catalyst in the synthesis of Core 6 and 7 mucin-type α-*O*-linked glycoconjugates. Overall, the results reported herein demonstrate that in addition to solvent effects and the influence of the nucleophile acceptor, a chiral organocatalyst can be used to affect the stereo-outcome of these glycosylation reactions. Efforts are currently underway to develop new and improved organocatalytic systems that can give us complete stereocontrol.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01962.

Experimental procedures and characterization data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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